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PATENT COOPERATION TREATY



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M/43127-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP2003/009452	International filing date (day/month/year) 26 August 2003 (26.08.2003)	Priority date (day/month/year) 26 August 2002 (26.08.2002)
International Patent Classification (IPC) or national classification and IPC C12P 13/04, 13/12		
Applicant BASF AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.	
2. This REPORT consists of a total of <u>10</u> sheets, including this cover sheet.	
<input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).	
These annexes consist of a total of _____ sheets.	
3. This report contains indications relating to the following items:	
I	<input checked="" type="checkbox"/> Basis of the report
II	<input type="checkbox"/> Priority
III	<input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	<input checked="" type="checkbox"/> Lack of unity of invention
V	<input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	<input type="checkbox"/> Certain documents cited
VII	<input type="checkbox"/> Certain defects in the international application
VIII	<input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 24 March 2004 (24.03.2004)	Date of completion of this report 09 December 2004 (09.12.2004)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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I. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
 pages _____ 1-39 _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☒ the claims:
 pages _____ 1-16 _____, as originally filed
 pages _____, as amended (together with any statement under Article 19
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☒ the drawings:
 pages _____ 1/3-3/3 _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☒ the sequence listing part of the description:
 pages _____ 1-92 _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

See Supplemental sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. _____

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

Lack of unity of invention

The Examining Authority has found that the international application comprises a number of inventions or groups of inventions not linked by a single general inventive concept (PCT Rule 13.1), that is to say:

I: Claims 1-14 and 16;

II: Claim 15.

The reasons are as follows:

The aim of **invention 1** is to provide a method for the fermentative production of a sulphur-containing fine chemical (L-methionine), which is achieved by the use of a culture of coryneform bacteria in which at least one heterologous nucleotide sequence coding for a protein with homoserine-O-acetyl-transferase (metA) activity is expressed.

The aim of **invention 2** is to provide an animal feed additive containing L-methionine from fermentation broths. This was accomplished by cultivating and fermenting any microorganism producing L-methionine, removing water and biomass and drying the resulting fermentation broth. Invention 2 contains no reference to invention 1.

Since inventions 1 and 2 solve different problems the solutions thereto are likewise different and not linked by a single general inventive concept.

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

The special technical features each of the inventions contributes to the prior art (use of a specific microorganism in invention 1; preparation of a fermentation broth of any microorganism for invention 2) likewise differ and therefore fail to meet the unity of invention requirement.

Since the PCT procedure was brief and owing to the fact that the additional search and substantive examination did not entail much outlay and that claim 15 in any event does not appear to be novel (see below), the applicant is not invited to pay additional fees in the international procedure.

However, this point will be raised in the regional procedure before the EPO.

Moreover, as regards the unity of invention, reference is made to the last paragraph in Box V below.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	4	YES
	Claims	1-3, 5-16	NO
Inventive step (IS)	Claims		YES
	Claims	1-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2. Citations and explanations

1). The international search report citations are numbered as follows:

D1: WO 02/10206 A (DEGUSSA) 7 February 2002 (2002-02-07)

D2: WO 02/18613 A (DEGUSSA) 7 March 2002 (2002-03-07)

D3: PARK S-D ET AL: "ISOLATION AND ANALYSIS OF META, A METHIONINE BIOSYNTHETIC GENE ENCODING HOMOSERINE ACETYLTRANSFERASE IN CORYNEBACTERIUM GLUTAMICUM" MOLECULAR AND CELLS, KOREAN SOCIETY FOR MOLECULAR SOCIETY, KR, Vol. 8, No. 3, 30 June 1998 (1998-06-30), pages 286-294, XP001002218.

D4: HWANG BYUNG-JOON ET AL: "Corynebacterium glutamicum utilizes both transsulfuration and direct sulfhydrylation pathways for methionine biosynthesis" JOURNAL OF BACTERIOLOGY, Vol. 184, No. 5, March 2002 (2002-03), pages 1277-1286, XP002269798 ISSN: 0021-9193.

2). The present application:

Claims 1-14 of the present application concern a

method for the fermentative production of a sulphur-containing fine chemical (L-methionine), wherein a culture of coryneform bacteria is used in which at least a heterologous nucleotide sequence coding for a protein with homoserine-O-acetyl-transferase (metA) activity is expressed.

Claim 15 concerns a method for producing an animal feed additive containing L-methionine from fermentation broths by cultivating and fermenting any microorganism producing L-methionine, removing water and biomass and drying the resulting fermentation broth.

Claim 16 makes use of the microorganisms used in the method according to claims 1-14, such that claim 16 is considered a multiple-step method incorporating claims 1-14.

The present application contains the following defects (PCT Article 5 and 6) which are significant for the substantive examination:

-) the expression "sulphur-containing fine chemical" in the claims (especially claim 1) and the description is so broad and undefined that it leaves the subject matter for which protection is sought in the claim unclear. In addition, it is clear from the description and the examples that only L-methionine is produced;
-) the feature "less than 100 % sequence homology" in claim 3 is meaningless because the scope of the claim includes *all* the sequences apart from the metA-coding sequence from *Corynebacterium*

glutamicum ATCC 13032. Consequently, claim 3 is too broad, vague and undefined and for the purpose of the substantive examination is interpreted in its broadest form;

-) claims 5 and 6 contain so-called functional definitions, that is to say, a feature is defined in terms of its function, that is, the result to be obtained by it. In the present case this objection pertains to the "homologous sequences" which are defined only in terms of their function and therefore require the user of the patent to make an unreasonable effort when testing for these functions.

The same objection is also raised with regard to claims 10-12, wherein the above kind of functional feature, that is, "... and is mutated in such way as to ..." leaves the subject matter for which protection is sought completely vague and undefined.

Claims 5, 6 and 10-12 are therefore vague and undefined and, in the light of the description, much too broad.

Since the term "homologous" is not defined *per se*, claims 5 and 6 are likewise interpreted as broadly as possible for the purpose of the examination.

3). Brief discussion of the prior art documents:

Document D1 describes the production of methionine using microorganisms during which the, *inter alia*,

metaA gene is (over)expressed (see, for example, claim 15 of document D1).

Document D1 further discloses methods for the production of an L-methionine-containing feed additive from fermentation broths, which comprises the same steps as the present claim 15 (see claim 19 in document D1). Document D1 is therefore prejudicial to the novelty of claims 1-3 and 5-16 of the application and relevant to the assessment with regard to inventive step of claims 1-16.

Document D2 discloses the production of "sulphur-containing fine chemicals" (especially L-lysine and L-methionine) with coryneform bacteria in which the metaA gene was overexpressed (see in particular page 10, claim 10 and example 6).

Since the gene used in document D2 (preferably from *C. glutamicum* ATCC 13032) can also have sequence changes - see, for example, page 5 and claims 1 and 5 in document D2 - document D2 is likewise relevant to those of the present claims which relate to a (non-specific) sequence homology. Further possible genetic modifications are disclosed on pages 13 and 14 of document D2.

Document D2 further discloses a method for producing an L-methionine-containing feed additive from fermentation broths which comprises the same steps as the present claim 15 (see claim 25 in document D2).

Document D2 is therefore likewise prejudicial to the novelty of claims 1-3 and 5-16, and relevant to the

heterologous nucleotide sequence coding for a protein with a homoserine-O-acetyl-transferase (metA) activity in the production of methionine is known (see documents D1 to D4). Although the bacterial strains listed in claim 4 are not mentioned in the above documents, these strains appear to be known for the fact (see the description, for example pages 13-15, of the present application) that they have a homoserine-O-acetyl-transferase (metA) activity. It is therefore not clear what advantage there might lie in using the above microorganisms as opposed to those known from the prior art.

The results of a comparative test disclosed on page 39 of the present application show only that the microorganism transformed with the metA gene has a higher activity. However, this is already known from the prior art (see page 12, line 8, of document D1).

No inventive step can therefore be recognized for the subject matter of claim 4.

As a precaution the examiner wishes to point out that, should the inventive step be considered to consist in the selection of these specific microorganisms, the selection of each individual microorganism would constitute a separate invention, such that claim 4 would result in 23 different inventions and hence not meet the unity of invention requirement.

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6). Industrial applicability (PCT Article 33(1) and (4)):

The subject matter of claims 1-16 is industrially applicable.



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